REMARKS

Applicant acknowledges and thanks the Examiner for the withdrawal of the previous indication of finality.

Applicant also acknowledges that the rejection of record under 35 U.S.C. §103 over Levine J.D., US 2004/0180916 has been withdrawn.

Claims 1, 11, 14-18, 21-32, 38, 39, 43, 45, 51-61, 64-70, 76, 77, 82-85, 88, 95, 96, 103, 104, 107-109 and 112-121 are under consideration.

Rejection under 35 U.S.C. §112

Claims 1, 11, 22-24, 27, 29, 31, 39, 61, 64, 65, 68, 77 and 113 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

Although the Examiner notes that the specification teaches that methylnaltrexone speeds up transit of material through the gut (Office Action of 01/13/2009, page 2), the Examiner alleges that sufficient guidance to support predictable operability of the invention is not present with respect to all claimed limitations. Specifically, the Examiner refers to the treatment of the symptoms of abdominal bloating, distention and stool consistency as well as methods comprising administering an opioid agonist to a patient. Applicant disagrees and respectfully requests reconsideration.

To satisfy the written description requirement an applicant must convey with reasonable clarity to those skilled in the art that , as of the filing date, he or she was in possession of the invention. The present specification states that constipation-predominant irritable bowel syndrome can be treated with methylnaltrexone (for example, see paragraphs [0019], [0023] and [0007] of the published specification). The limitations in question are known symptoms of irritable bowel syndrome. For example, the symptoms of bloating, distention and stool consistency are described in the published specification (see paragraphs [0002], [0023], and [0034]), and in claims 23, 24, 26, 64, 65 and 67 as originally filed.

The methods comprising the administration of an opioid agonist in addition to opioid antagonist are also described in the instant specification in claims 29 and 74 as originally filed, for example, and paragraphs [0028], [0029], [0035] and [0090] of the published specification.

Therefore, the filed specification provides sufficient description of the instant invention and the claimed limitations to reasonably convey to the skilled artisan that the Applicant was in possession of the claimed limitations at the time of filing of the instant application.

Given that the claim limitations discussed herein are explicitly described in the instant application, Applicant respectfully points out that the Examiner has not made a *prima facie* case for rejecting the claims on the basis of lack of written description by simply alleging the absence of sufficient guidance to support predictable operability. The Examiner has not offered any reason why the instant specification would fail to convey to one of ordinary skill in the art that Applicant had possession of the invention as of the filing date.

It respectfully is requested that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

Double Patenting Rejections

Claims 1, 11, 14-18, 21-32, 38, 39, 43, 45, 51-61, 64-70, 76, 77, 82-85, 88, 95, 96, 103, 104, 107-109 and 112-121 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 66 and 92 of co-pending U.S. Patent Application No. 11/441,452. Claims 66 and 92 in U.S. Patent Application No. 11/441,452 have already been canceled and are no longer pending. Therefore, Applicant submits that the rejection is rendered moot.

Claims 1, 11, 14-18, 21-32, 38, 39, 43, 45, 51-61, 64-70, 76, 77, 82-85, 88, 95, 96, 103, 104, 107-109 and 112-121 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 118-120 and 141-143 of co-pending U.S. Patent Application No. 11/441,395. Claims 118-120 and 141-143 of co-pending U.S.

Patent Application No. 11/441,395 have already been canceled and are no longer pending. Therefore, Applicant submits that the rejection is rendered moot.

Rejections under 35 U.S.C. §103(a)

Claims 1, 11, 14-18, 21-32, 38, 39, 43, 45, 51-61, 64-70, 76, 77, 82-85, 88, 95, 96, 103, 104, 107-109 and 112-121 are rejected under 35 U.S.C. §103(a) as being unpatentable over Minoia et al., US Patent No. 5,811,451 (herein Minoia).

Applicant respectfully requests reconsideration. At the time of the filing of the instant application, it was generally believed that the central nervous system plays an important role in the pathology of irritable bowel syndrome (see, for example, the discussion in paragraph [006] of the Background section of the published application). As stated in the application, the role of the central nervous system was strongly suggested by the clinical association of emotional disorders with irritable bowel syndrome symptoms. Further, as stated in the application, the role of the central nervous system also was strongly suggested by the existence of irritable bowel syndrome treatments that act on cerebral cortical sites. One of ordinary skill in the art would have been looking for centrally acting drugs to treat irritable bowel syndrome.

Minoia does not contradict the teachings of the prior art respecting the role of the central nervous system in irritable bowel syndrome. Minoia discloses irritable bowel syndrome in a lengthy list of endorphine-mediated pathologies. This list includes central nervous system conditions. Minoia also discloses methylnaltrexone in a list of opioid antagonists, which list includes both centrally and peripherally acting antagonists, and it would have been clear to one of ordinary skill in the art that the selection of the opioid antagonist would depend upon whether a centrally acting drug was indicated. Minoia does not specifically single out or suggest a peripheral opioid antagonist, such as methylnaltrexone, as a candidate for the treatment of irritable bowel syndrome.

Based on Minoia and in view of the state of the art as a whole at the time of filing of the instant application, a person of ordinary skill in the art would have selected from Minoia's list of

opioid antagonists a centrally acting antagonist for attempting to treat irritable bowel syndrome. The skilled person would have had no reason to select a peripheral opioid antagonist such as methylnaltrexone. It is only with impermissible hindsight that one would conclude that Minoia, taken with the art as a whole, suggests the present invention. Therefore, the instant invention is not obvious in view of the teaching of Minoia. Applicant respectfully requests withdrawal of the rejection over Minoia under 35 U.S.C. §103(a).

Claims 1, 11, 14-18, 21-32, 38, 39, 43, 45, 51-61, 64-70, 76, 77, 82-85, 88, 95, 96, 103, 104, 107-109 and 112-121 are rejected under 35 U.S.C. §103(a) as being unpatentable over Rhodes et al., U.S. Patent No. 6,734,188 in view of Drell et al., WO 99/22737.

The Examiner alleges that in view of the combined teachings of Rhodes and Drell, one skilled in the art would have been motivated to administer methylnaltrexone to treat irritable bowel syndrome because methylnaltrexone reduces the occurrence of side effects following administration of centrally acting agents. Applicant respectfully requests reconsideration.

Rhodes suggests that irritable bowel syndrome can be treated by delayed and sustained release dosage forms of opioid antagonists. In describing the opioid antagonists potentially useful in the Rhodes treatments, Rhodes focuses on centrally acting opioid antagonists. Rhodes states, " [p]referred opioid antagonists are naloxone and naltrexone". The only mention of methylnaltrexone in Rhodes is in the Background, where the prior art reference Drell is summarized and is said to disclose a method for treating or preventing a range of conditions, often side effects (e.g., constipation) from the use of opioid analgesics, by administering a quaternary derivative of noroxymorphone (e.g., methylnaltrexone; see column 2). The authors of Rhodes, therefore, were clearly aware of methylnaltrexone and its activity as an opioid antagonist. Yet, when these authors list the opioid antagonists useful in the practice of their invention ((see column 3, claim 14), methylnaltrexone is not on the list. Thus, it cannot be said that Rhodes in combination with Drell teach or suggest the use of methylnaltrexone in the treatment of IBS.

Secondly, if a person skilled in the art, starting from Rhodes, were to look for further opioid antagonists that are of use in treating irritable bowel syndrome, then that person would be inclined to select opioid antagonists with high affinity for opioid receptors so that the opioid antagonist would be effective. For example, as stated in Brown D. R. and Goldberg L. I. (1985) *Neuropharmacology* vol 24, no 3, (copy enclosed with this letter for the examiner's ease of reference), "...quaternization of the opiate antagonists generally greatly diminished their affinity for opiate receptors. For example, methylnaloxone has generally been found to posses only 2 to 4% of the opiate antagonist activity of naloxone *in vitro* and potency differences between methylnaltrexone and naltrexone are of the same order ..." (page 182, lines 24 to 31). Brown et al. continue, "..[a] seeming lack of pharmacological effect may be due to the relatively low affinity of these quaternary compounds for opiate receptors" (page 183, lines 44 to 47). Therefore a person skilled in the art would be unlikely to choose methylnaltrexone as an effective irritable bowel syndrome treatment.

Applicant respectfully requests withdrawal of instant rejection under 35 U.S.C. §103(a) over Rhodes in view of Drell.

Conclusion

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 23/2825 under Docket No. P0453.70112US01 from which the undersigned is authorized to draw.

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Respectfully submitted,

By _____

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